(FILE 'HOME' ENTERED AT 15:29:11 ON 21 DEC 1999)

FILE 'EMBASE, MEDLINE, BIOSIS, CAPLUS, SCISEARCH, TOXLINE, CANCERLIT, APIPAT, CROPU, DGENE, DPCI, EUROPATFULL, IFIPAT, INPADOC, JAPIO, PAPERCHEM2, PATDD, PATDPA, PATOSDE, PATOSEP, PATOSWO, PIRA, RAPRA, TULSA,
TULSA2, USPATFULL' ENTERED AT 15:30:20 ON 21 DEC 1999

L1 615 S (BAG(3A)(GENE OR PROTEIN#))
L2 88 S L1 (30A) (CANCER OR CARCINOMA OR TUMOUR OR TUMOR OR MALIGNAN
L3 32 DUP REM L2 (56 DUPLICATES REMOVED)

L3 ANSWER 11 OF 32 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 1999:493789 SCISEARCH
GA The Genuine Article (R) Number: 196PK
TI Expression patterns and subcellular distribution of the anti-apoptotic **protein Bag**-1 in normal and **malignant** oral epithelium: relation to cellular differentiation and prognosis for oral squamous cell **carcinoma**.
AU Hague A (Reprint); Packham G; Huntley S; Heung Y L
CS UNIV BRISTOL, DEPT ORAL & DENT SCI, BRISTOL, AVON, ENGLAND; IMPERIAL COLL ST MARYS, LUDWIG INST CANC RES, LONDON W2 1PG, ENGLAND
CYA ENGLAND
SO JOURNAL OF DENTAL RESEARCH, (MAY 1999) Vol. 78, No. 5, pp. 1082-1082. Publisher: AMER ASSOC DENTAL RESEARCH, 1619 DUKE ST, ALEXANDRIA, VA 22314.
ISSN: 0022-0345.
DT Conference; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 0
TI Expression patterns and subcellular distribution of the anti-apoptotic **protein Bag**-1 in normal and **malignant** oral epithelium: relation to cellular differentiation and prognosis for oral squamous cell **carcinoma**.

L3 ANSWER 12 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 4
AN 1999293002 EMBASE
TI Overexpression of anti-apoptotic **gene BAG**-1 in human cervical **cancer**.
AU Yang X.; Hao Y.; Ferenczy A.; Tang S.-C.; Pater A.
CS A. Pater, Division of Basic Medical Sciences, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Nfld. A1B 3V6, Canada. apater@morgan.ucs.mun.ca
SO Experimental Cell Research, (25 Feb 1999) 247/1 (200-207).
Refs: 52
ISSN: 0014-4827 CODEN: ECREAL
CY United States
DT Journal; Article
FS 010 Obstetrics and Gynecology
016 Cancer
022 Human Genetics
LA English
SL English
AB Apoptosis is a programmed cell death process in which cells commit suicide under certain environmental conditions. Recent studies suggest that apoptosis is controlled by a variety of cellular genes, and dysregulation of these genes plays an important role in the pathogenesis of human diseases, including cancer. BAG-1 is a novel anti-apoptotic protein isolated by its interaction with another anti-apoptotic protein, Bcl-2. It binds to several hormone receptors and growth factor receptors and modulates their function in apoptosis. However, the role of BAG-1 in the oncogenesis of human cervical cancer has yet to be illustrated. In this study, we examined the expression of BAG-1 in cervical normal and carcinoma cultured cells and tissues. BAG-1 was overexpressed in human cervical carcinoma cell lines and tissues. Overexpression was regulated at the transcriptional level. The increased expression of BAG-1 was correlated with enhanced resistance of cervical carcinoma cells to

apoptosis induced by a DNA-damaging reagent. In addition, overexpression of BAG-1 enhanced the resistance of cervical cells to apoptosis. This study provided the first evidence that BAG-1 is upregulated in human cervical cancer and may play an important role in apoptosis and human cervical carcinogenesis.

TI Overexpression of anti-apoptotic **gene BAG**-1 in human cervical **cancer**.

L3 ANSWER 13 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 5
AN 1999150399 EMBASE
TI Prognostic significance of apoptosis regulators in breast cancer.
AU Krajewski S.; Krajewska M.; Turner B.C.; Pratt C.; Howard B.; Zapata J.M.;
Frenkel V.; Robertson S.; Ionov Y.; Yamamoto H.; Perucho M.; Takayama S.; Reed J.C.
CS S. Krajewski, Burnham Institute, Program on Apoptosis/Cell Death Res., 10901 North Torrey Pines Road, San Diego, CA 92037, United States
SO Endocrine-Related Cancer, (1999) 6/1 (29-40).
Refs: 78
ISSN: 1351-0088 CODEN: ERCAE
CY United Kingdom
DT Journal; General Review
FS 003 Endocrinology
005 General Pathology and Pathological Anatomy
016 Cancer
LA English
SL English
AB Dysregulation of normal programmed cell death mechanisms plays an important role in the pathogenesis and progression of breast cancer, as well as in responses of tumors to therapeutic intervention. Overexpression of anti-apoptotic members of the Bcl-2 family such as Bcl-2 and Bcl-x(L) has been implicated in cancer chemoresistance, whereas high levels of pro-apoptotic proteins such as Bax promote apoptosis and sensitize tumor cells to various anticancer therapies. Though the mechanisms by which Bcl-2 family proteins regulate apoptosis are diverse, ultimately they govern decision steps that determine whether certain caspase family cell death proteases remain quiescent or become active. To date, approximately 17 cellular homologs of Bcl-2 and at least 15 caspases have been identified in mammals. Other types of proteins may also modulate apoptotic responses through effects on apoptosis-regulatory proteins, such as BAG-1 - a heat shock protein 70 kDa (Hsp70/Hsc70)-binding protein that can modulate stress responses and alter the functions of a variety of proteins involved in cell death and division. In this report, we summarize our attempts thus far to explore the expression of several Bcl-2 family **proteins**, caspase-3, and **BAG**-1 in primary breast **cancer** specimens and breast **cancer** cell lines. Moreover, we describe some of our preliminary observations concerning the prognostic significance of these apoptosis regulatory proteins in breast **cancer** patients, contrasting results derived from women with localized disease (with or without node involvement) and metastatic cancer.
AB . . . death and division. In this report, we summarize our attempts thus far to explore the expression of several Bcl-2 family **proteins**, caspase-3, and **BAG**-1 in primary breast **cancer** specimens and breast **cancer** cell lines. Moreover, we describe some of our preliminary observations concerning the prognostic significance of these apoptosis regulatory proteins in breast **cancer** patients, contrasting results derived from women with localized disease (with or without node involvement) and metastatic

L3 ANSWER 15 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 6
AN 1998227564 EMBASE
TI Interaction of BAG-1 with retinoic acid receptor and its inhibition of retinoic acid-induced apoptosis in cancer cells.
AU Liu R.; Takayama S.; Zheng Y.; Froesch B.; Chen G.-Q.; Zhang X.; Reed J.C.; Zhang X.-K.
CS X.-K. Zhang, Burnham Institute, Cancer Research Center, 10901 N. Torrey Pines Rd., San Diego, CA 92037, United States. xzhang@ljcrf.edu
SO Journal of Biological Chemistry, (3 Jul 1998) 273/27 (16985-16992).
Refs: 52
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
LA English
SL English
AB BAG-1 (also known as HAP46) is an anti-apoptotic protein, which has been shown previously to interact with a number of nuclear hormone receptors, including receptors for glucocorticoid, estrogen, and thyroid hormone. We show here that BAG-1 also interacts with retinoic acid receptor (RAR). Gel
retardation assays demonstrated that in vitro translated BAG-1 protein could effectively inhibit the binding of RAR but not retinoid X receptor (RXR) to a number of retinoic acid (RA) response elements (RAREs). A glutathione S- transferase-BAG-1 fusion protein also specifically bound RAR but not RXR. Interaction of BAG-1 and RAR could also be demonstrated by yeast two-hybrid assays. In transient transfection assays, co-transfection of BAG-1 expression plasmid inhibited the transactivation activity of RAR/heterodimers but not RXR/RXR homodimers. When stably expressed in breast cancer cell lines, BAG-1 inhibited binding of RAR/RXR heterodimer to a number of RAREs and suppressed RA-induced growth inhibition and apoptosis. In addition, RA-induced suppression of Bcl-2 expression was abrogated by overexpression of BAG-1. These results demonstrate that BAG-1 can regulate retinoid activities through its interaction with RAR and suggest that elevated levels of **BAG**-1 **protein** could potentially contribute to retinoid resistance in **cancer** cells.
AB . . . These results demonstrate that BAG-1 can regulate retinoid activities through its interaction with RAR and suggest that elevated levels of **BAG**-1 **protein** could potentially contribute to retinoid resistance in **cancer** cells.

L3 ANSWER 16 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 7
AN 1998197198 EMBASE
TI BAG-1L protein enhances androgen receptor function.
AU Froesch B.A.; Takayama S.; Reed J.C.
CS J.C. Reed, Burnham Institute, 10901 N. Torrey Pines Rd., San Diego, CA 92037, United States. jreed@burnham-inst.org
SO Journal of Biological Chemistry, (8 May 1998) 273/19 (11660-11666).
Refs: 41
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
LA English
SL English
AB BAG-1 is a regulator of heat shock protein (Hsp) 70/Hsc70 family proteins

that interacts wi[redacted]steroid hormone receptors. The[redacted]cently identified BAG-1 long (**BAG**-1L) **protein**, an isoform of **BAG**-1 that arises from translation initiation at a noncanonical CUG codon, was co-immunoprecipitated with androgen receptors (AR) from LNCaP prostate **cancer** cells and other cell lysates, whereas the shorter originally identified BAG-1 and **BAG**-1M (RAP 46) **proteins** were not. **BAG**-1L, but not BAG-1 or BAG-1M (RAP46), also markedly enhanced the ability of AR to transactivate reporter gene plasmids containing an androgen response element (ARE) in PC3 prostate **cancer** and other cell lines. A C-terminal region deletion mutant of BAG-1L failed to co- immunoprecipitate with AR and functioned as a trans-dominant inhibitor of BAG-1L, impairing AR-induced transactivation of ARE-containing reporter plasmids. In addition, BAG-1L significantly reduced the concentrations of 5.alpha.-dihydrotestosterone (DHT) required for AR activity but did not induce ligand-independent transactivation. BAG-1L also markedly improved the ability of AR to transactivate reporter genes when cells were cultured with DHT in combination with the anti-androgen cyproterone acetate. The effects of BAG- 1L on AR could not be explained by detectable alterations in the DHT-induced translocation of AR from cytosol to nucleus, nor by BAG-1L-induced increases in the amounts of AR **protein**. These findings implicate **BAG**-1L in the regulation of AR function and may have relevance to mechanisms of prostate **cancer** resistance to hormone-ablative and anti-androgen therapy.

AB . . . regulator of heat shock protein (Hsp) 70/Hsc70 family proteins that interacts with steroid hormone receptors. The recently identified BAG-1 long (**BAG**-1L) **protein**, an isoform of **BAG**-1 that arises from translation initiation at a noncanonical CUG codon, was co-immunoprecipitated with androgen receptors (AR) from LNCaP prostate **cancer** cells and other cell lysates, whereas the shorter originally identified BAG-1 and **BAG**-1M (RAP 46) **proteins** were not. **BAG**-1L, but not BAG-1 or BAG-1M (RAP46), also markedly enhanced the ability of AR to transactivate reporter gene plasmids containing an androgen response element (ARE) in PC3 prostate **cancer** and other cell lines. A C-terminal region deletion mutant of BAG-1L failed to co- immunoprecipitate with AR and functioned as. . . alterations in the DHT-induced translocation of AR from cytosol to nucleus, nor by BAG-1L-induced increases in the amounts of AR **protein**. These findings implicate **BAG**-1L in the regulation of AR function and may have relevance to mechanisms of prostate **cancer** resistance to hormone-ablative and anti-androgen therapy.

L3 ANSWER 17 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 8
AN 1998243196 EMBASE
TI Expression and location of Hsp70/Hsc-binding anti-apoptotic **protein BAG**- 1 and its variants in normal tissues and **tumor** cell lines.
AU Takayama S.; Krajewski S.; Krajewska M.; Kitada S.; Zapata J.M.; Kristine Z.; Kochel K.; Knee D.; Scudiero D.; Tudor G.; Miller G.J.; Miyashita T.; Yamada M.; Reed J.C.
CS J.C. Reed, Burnham Institute, 10901 North Torrey Pines Road, San Diego, CA 92037, United States. jreed@burnham-inst.org
SO Cancer Research, (15 Jul 1998) 58/14 (3116-3131).
Refs: 32
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer

LA English
SL English
AB BAG-1 is a multifunctional protein that blocks apoptosis and interacts with several types of proteins, including Bcl-2 family proteins, the kinase Raf-1, certain tyrosine kinase growth factor receptors, and steroid hormone receptors, possibly by virtue of its ability to regulate the Hsp70/Hsc70 family of molecular chaperones. Two major forms of the human and mouse BAG-1 proteins were detected by immunoblotting. The longer human and mouse BAG-1 proteins (BAG-1L) appear to arise through translation initiation at noncanonical CTG codons located upstream of and in-frame with the usual ATG codon used for production of the originally described BAG-1 protein. Immunoblotting experiments using normal tissues revealed that BAG-1L is far more restricted in its expression and is present at lower levels than the more prevalent BAG-1 protein. Human but not mouse tissues also produce small amounts of an additional isoform of BAG-1 of intermediate size (BAG-1M) that probably arises through translation initiation at yet another site involving an ATG codon. All three isoforms of human BAG-1 (BAG-1, BAG-1M, and BAG-1L) retained the ability to bind Hsc70. Subcellular fractionation and immunofluorescence confocal microscopy studies indicated that BAG-1L often resides in the nucleus, consistent with the presence of a nuclear localization sequence in the NH2-terminal unique domain of this protein. In immunohistochemical assays, BAG-1 immunoreactivity was detected in a wide variety of types of cells in normal adult tissues and was localized to either cytosol, nucleus, or both, depending on the particular type of cell. In some cases, cytosolic BAG-1 immunostaining was clearly associated with organelles resembling mitochondria, consistent with the reported interaction of BAG-1 with Bcl-2 and related proteins. Furthermore, experiments using a green fluorescence protein (GFP)-BAG-1 fusion protein demonstrated that overexpression of Bcl-2 in cultured cells can cause intracellular redistribution of GFP-BAG-1, producing a membranous pattern typical of Bcl-2 family **proteins**. The **BAG**-1 **protein** was found at high levels in several types of human **tumor** cell lines among the 67 tested, particularly leukemias, breast, prostate, and colon cancers. In contrast to normal tissues, which only rarely expressed BAG-1L, **tumor** cell lines commonly contained **BAG**-1L **protein**, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies **malignant** transformation.
TI Expression and location of Hsp70/Hsc-binding anti-apoptotic **protein BAG**- 1 and its variants in normal tissues and **tumor** cell lines.
AB . . . overexpression of Bcl-2 in cultured cells can cause intracellular redistribution of GFP-BAG-1, producing a membranous pattern typical of Bcl-2 family **proteins**. The **BAG**-1 **protein** was found at high levels in several types of human **tumor** cell lines among the 67 tested, particularly leukemias, breast, prostate, and colon cancers. In contrast to normal tissues, which only rarely expressed BAG-1L, **tumor** cell lines commonly contained **BAG**-1L **protein**, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies **malignant** transformation.

L3 ANSWER 18 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 9
AN 1998:305490 BIOSIS
DN PREV199800305490
TI Prolonged cell survival enhances peritoneal dissemination of gastric cancer cells.
AU Yawata, Atsushi; Adachi, Masaaki (1); Okuda, Hiroyuki; Naishiro, Yasuyoshi; Takamura, Takenori; Hareyama, Masato; Takayama, Shinichi; Reed,

John C.; Imai, Ko[redacted]h
CS (1) First Dep. Int[redacted]n. Med., Sapporo Med. Univ. Sch. Med., Sapporo 060 Japan
SO Oncogene, (May 21, 1998) Vol. 16, No. 20, pp. 2681-2686.
ISSN: 0950-9232.
DT Article
LA English
AB Bcl-2 and a Bcl-2-binding protein BAG-1 function in protection from apoptosis induced by a variety of stimuli. Deregulated expression of Bcl-2 leads to inhibition of apoptosis and is correlated with development of various cancers. Here, we provide evidence that prolonged cell survival introduced by overproduction of Bcl-2 or BAG-1 strongly enhances peritonea) dissemination of human gastric cancer MKN74 cells. Gene transfer-mediated overexpression of Bcl-2 or BAG-1 led to prolonged cell survival of MKN74 cells against serum-starved apoptosis and anoikis. When the viable transfectants were inoculated into the intraperitoneal cavity of BALB/c nude mice, the Bcl-2-expressing MKN74 cells and the BAG-1-expressing MKN74 cells exhibited strongly enhanced peritoneal dissemination in BALB/c nude mice and whole disseminated tumor weights were increased by 4-fold and 3.3-fold, respectively, compared with the control transfectants. The enhanced peritoneal dissemination of MKN74-Bcl-2 and MKN74-BAG-1 transfectants correlated well with resistance to cell death induced by serum-starvation and anoikis. However, the overexpression of Bcl-2 or BAG-1 caused no significant difference among the transfectants in cell growth rates, either in vitro or in vivo. Taken together, these studies demonstrate that resistance to apoptosis is a crucial factor for development of peritoneal dissemination of human gastric cancer cells.
IT Major Concepts
Tumor Biology
IT Chemicals & Biochemicals

L3 ANSWER 20 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 11
AN 1998312706 EMBASE
TI Human **BAG**-1/RAP46 **protein** is generated as four isoforms by alternative translation initiation and overexpressed in **cancer** cells.
AU Yang X.; Chernenko G.; Hao Y.; Ding Z.; Pater M.M.; Pater A.; Tang S.-C.
CS S.-C. Tang, Basic Medical Sciences, Faculty of Medicine, Memorial University of Newfoundland, 300 Prince Philip Drive, St John's, Nfld. A1B 3V6, Canada
SO Oncogene, (27 Aug 1998) 17/8 (981-989).
Refs: 27
ISSN: 0950-9232 CODEN: ONCNES
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
LA English
SL English
AB Previously, a Bcl-2-interacting protein, BAG-1, was cloned from mouse cells and was shown to interact with several other proteins and to be important for inhibition of apoptosis. Human BAG-1 (hBAG-1) cDNA, recently isolated by us and two other groups, has been shown to be identical to a hormone receptor-binding protein, RAP46. However, different molecular masses of hBAG-1 protein products were noted by these three groups. Here we demonstrated that hBAG-1 protein was expressed as four isoforms, designated p50, p46, p33 and p29, with apparent molecular masses of 50 kDa, 46 kDa, 33 kDa and 29 kDa, respectively. Deletion, site-directed mutagenesis and in vitro transcription/translation analysis showed that the four protein products of hBAG-1 were expressed by alternative initiation from four different start codons through a leaky scanning mechanism. Furthermore, we demonstrated that the distinct forms of hBAG-1 have different subcellular localizations, suggesting that they may have distinct functions in the cells. Characterization of hBAG-1 RNA and protein also showed that hBAG-1 was overexpressed in human cervical, breast and lung cancer cell lines. Taken together, these data clarify the conflicting observations reported in the literature and suggest that hBAG-1 is expressed as four forms of protein products, which may play a differential role in apoptosis and oncogenesis of human cells.
TI Human **BAG**-1/RAP46 **protein** is generated as four isoforms by alternative translation initiation and overexpressed in **cancer** cells.

L3 ANSWER 21 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998084196 EMBASE
TI Molecular targeting therapy for cancer.
AU Hinoda Y.; Naeshiro Y.; Imai K.
CS Dr. Y. Hinoda, First Dept. of Internal Medicine, Sapporo Medical University, Minami-1-jo Nishi-16-chome, Chuo-ku, Sapporo 060-0061, Japan
SO Biotherapy, (1998) 12/2 (290-296).
Refs: 20
ISSN: 0914-2223 CODEN: BITPE
CY Japan
DT Journal; Article
FS 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
LA Japanese
SL English; Japanese

AB The mechanisms of [redacted]rcinogenesis and cancer develo[redacted]nt have recently been clarified at the molecular level. It is now possible to develop a cancer therapy to regulate the expression of a molecule as a therapeutic target. MUC1 mucin is considered to be an important therapeutic target molecule from two viewpoints. One is the inducibility of HLA-unrestricted and MUC1-specific cytotoxic T lymphocytes in various cancer patients. Their ex vivo expansion against autologous MUC1 cDNA transfected B-cells is expected to be applicable for cancer therapy. The other is a possible role of MUC1 mucin in cancer invasion. Recent immunohistochemical findings have suggested that MUC1 is predominantly expressed in a type of invasive cancer. Both in vitro and in vivo invasiveness of gastric cancer MKN74 cells was increased by MUC1 cDNA transfection. KAI1 was cloned as a metastasis suppressor gene for prostate cancer. Recent evidences have suggested that KAI1 may behave as a metastasis suppressor in various cancers other than prostate **cancer**. Decreased motility and invasiveness of colon **cancer** cells resulted in KAI1 cDNA transfection. Bcl-2 is known to inhibit apoptosis from a variety of stimuli. A Bcl-2- binding **protein BAG**-1 also functions to protect against apoptosis in concert with Bcl-2. We provided evidences that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG**-1 **proteins** strongly promotes experimental pulmonary **metastasis** of melanoma cells. The development of more effective regulators for those gene expressions and of vectors with targeting function will facilitate clinical application of molecular targeting therapy for cancer.

AB . . . prostate cancer. Recent evidences have suggested that KAI1 may behave as a metastasis suppressor in various cancers other than prostate **cancer**. Decreased motility and invasiveness of colon **cancer** cells resulted in KAI1 cDNA transfection. Bcl-2 is known to inhibit apoptosis from a variety of stimuli. A Bcl-2- binding **protein BAG**-1 also functions to protect against apoptosis in concert with Bcl-2. We provided evidences that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG**-1 **proteins** strongly promotes experimental pulmonary **metastasis** of melanoma cells. The development of more effective regulators for those gene expressions and of vectors with targeting function will. . .

L3 ANSWER 22 OF 32 CAPLUS COPYRIGHT 1999 ACS
AN 1998:136934 CAPLUS
DN 128:255783
TI Expression of multiple apoptosis-regulatory genes in human breast cancer cell lines and primary tumors
AU Zapata, Juan M.; Krajewska, Maryla; Krajewski, Stanislaw; Huang, Ruo-Pan; Takayama, Shinichi; Wang, Hong-Gang; Adamson, Eileen; Reed, John C.
CS Cancer Research Center, Oncogene & Tumor Suppressor Gene Program, The Burnham Inst., La Jolla, CA, 92037, USA
SO Breast Cancer Res. Treat. (1998), 47(2), 129-140
CODEN: BCTRD6; ISSN: 0167-6806
PB Kluwer Academic Publishers
DT Journal
LA English
AB The expression of several apoptosis-regulating genes was evaluated in 9 human breast cancer cell lines, 2 immortalized human mammary epithelial lines, 1 normal breast tissue biopsy, and 3 primary breast tumors, using a multiple antigen detection (MAD) immunoblotting method. The anti-apoptotic proteins Bcl-2, Bcl-XL Mcl-1, and BAG-1 were present at immunodetectable levels in 7, 10, 10, and 9 of the 11 lines. Comparing these 11 cell lines among themselves revealed that steady-state levels of Bcl-2, Bcl-XL Mcl-1, and BAG-1 were present at relatively higher levels in

4, 6, 5, and 5 of [redacted] lines, resp. In contrast, t[redacted]ro-apoptotic proteins Bax and Bak were detected in all 11 cell lines, and were present at relatively higher levels in 10 and 5 of the 11 lines, resp. The Interleukin-1.beta. converting enzyme (ICE) homolog CPP32 (Caspase-3) was expressed in 10/11 breast cell lines. High levels of p53 protein, indicative of mutant p53, were found in 8 of the 11 lines and correlated inversely with Bax expression. Bcl-2 and BAG-1 protein levels were pos. correlated. Immunoblot anal. of primary adenocarcinomas revealed expression of the anti-apoptotic proteins Bcl-2, Bcl-XL Mcl-1, and BAG-1, as well as the pro-apoptotic proteins Bax, Bak, and CPP32, in at least 2 of the 3 tumors examd. Immunohistochem. anal. was also performed for all of these proteins using 20 paraffin-embedded breast cancer biopsy specimens that all contained residual normal mammary epithelium in combination with both invasive cancer and carcinoma in situ. All of these apoptosis-regulating proteins were detected in primary breast cancers, though the percentage of immunopos. tumor cells varied widely in some cases. Comparisons of the intensity of immunostaining in normal mammary epithelium and invasive carcinoma suggested that Bcl-2 immunointensity tends to be lower in cancers than normal breast epithelium, whereas CPP32 immunointensity was generally higher in invasive cancers. The results demonstrate expression of multiple apoptosis-modulating proteins in breast cancer cell lines and primary tumors, suggesting complexity in the regulation of apoptosis in these neoplasms of mammary epithelial origin.

IT Proteins (specific **proteins** and subclasses)
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**gene BAG**-1; expression of multiple apoptosis-regulatory genes in human breast **cancer** cell lines and primary tumors)

L3 ANSWER 23 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:364793 BIOSIS
DN PREV199800364793
TI Enhanced expression of anti-apoptotic proteins in human papillomavirus-immortalized and cigarette smoke condensate-transformed human endocervical cells: Correlation with resistance to apoptosis induced by DNA damage.
AU Yang, Xiaolong; Hao, Yawei; Pater, Mary M.; Tang, Shou-Ching; Pater, Alan (1)
CS (1) Div. Basic Med. Sci., Fac. Med., Memorial Univ. Newboundland, St. John's, Newfoundland A1B 3V6 Canada
SO Molecular Carcinogenesis, (June, 1998) Vol. 22, No. 2, pp. 95-101. ISSN: 0899-1987.
DT Article
LA English
AB Apoptosis plays an important role in various biological processes including embryogenesis, differentiation, homeostasis, and oncogenesis. We have developed a system composed of primary human endocervical cells (HEN), HEN immortalized by human papillomavirus (HPV) type 16, and their counterparts subsequently malignantly transformed by cigarette smoke condensate (CSC). To understand the role of apoptosis in the multistep oncogenesis of human cervical cells, we examined the expression of apoptosis-associated proteins in our in vitro model system. The results showed no significant difference in the levels of apoptosis-inducing proteins bak and bax among all the cell types examined. On the other hand, the levels of apoptosis-inhibiting proteins bcl-2, bcl-xL and BAG-1 increased progressively after immortalization and transformation. The p53 protein level decreased in the HPV16-immortalized HEN and increased in one of two lines of the CSC-transformed HEN. Further, the increased levels of apoptosis-inhibiting proteins in the HPV16-immortalized and the

CSC-transformed H[redacted] correlated with progressively [redacted]reased resistance of these cells to ap[redacted]osis induced by staurosporine or cisplatin. This study
provided the first evidence that overexpression of apoptosis-inhibiting proteins is important for both multistep oncogenesis and resistance of human endocervical cells to apoptosis induced by DNA-damaging reagents.

IT . . .

damage-induced apoptosis resistance correlation, enhanced tumor cell expression; bcl-2 anti-apoptotic protein: DNA damage-induced apoptosis resistance correlation, enhanced tumor cell expression; **BAG**-1 anti-apoptotic **protein**: DNA damage-induced apoptosis resistance correlation, enhanced **tumor** cell expression

L3 ANSWER 27 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 12
AN 97225294 EMBASE
DN 1997225294
TI Anti-cell death activity promotes pulmonary metastasis of melanoma cells.
AU Takaoka A.; Adachi M.; Okuda H.; Sato S.; Yawata A.; Hinoda Y.; Takayama S.; Reed J.C.; Imai K.
CS M. Adachi, First Department Internal Medicine, Sapporo Medical University, School of Medicine, Sapporo 060, Japan
SO Oncogene, (1997) 14/24 (2971-2977).
Refs: 29
ISSN: 0950-9232 CODEN: ONCNES
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
LA English
SL English
AB Bcl-2 inhibits apoptosis from a variety of stimuli, and a Bcl-2-binding protein BAG-1 also functions in protection from apoptosis in concert with Bcl-2. Here, we provide evidence that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG**-1 **proteins** strongly promotes experimental pulmonary **metastasis** of melanoma B16-BL6 cells. In murine melanoma cell line B16-BL6, gene transfer-mediated expression of the Bcl-2 or BAG-1 led to prolonged cell survival against serum-starved apoptosis in vitro. The Bcl-2-expressing B16 cells, B16-Bcl-2 and the BAG-1-expressing B16 cells, B16-BAG-1 strongly enhanced pulmonary metastasis in allogenic BALB/c nude mice and whole lung weights were increased by 2.4-fold and 1.4-fold, respectively, compared with control transfectants, suggesting that Bcl-2 is a stronger positive modulator of metastasis. When the viable B16-Bcl-2 and control transfectants were injected subcutaneously into BALB/c nude mice, the colony numbers of pulmonary metastasis of the B16-Bcl-2 transfectant increased by 5.6-fold compared with the control transfectants. These enhanced metastatic potentials in the B16-Bcl-2 and the B16-BAG-1 transfectants were well correlated with anti-cell death activity against serum-starvation and enhanced cell viability on limiting dilution. Analysis of the transfectants however revealed that their growth rates, invasive ability and cell motility were not significantly altered by overexpression of either Bcl-2 or **BAG**-1 **proteins**. Taken together, these studies demonstrate that prolonged cell survival is a crucial factor to promote **metastasis** of melanoma, thereby contributing to **tumor** progression.
AB . . . from apoptosis in concert with Bcl-2. Here, we provide evidence that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG**-1 **proteins** strongly promotes experimental pulmonary **metastasis** of melanoma B16-BL6 cells. In murine melanoma cell line B16-BL6, gene transfer-mediated expression of the Bcl-2 or BAG-1 led to. . . . revealed that their growth rates, invasive ability and cell motility were not significantly altered by overexpression of either Bcl-2 or **BAG**-1 **proteins**. Taken together, these studies demonstrate that prolonged cell survival is a crucial factor to promote **metastasis** of melanoma, thereby contributing to **tumor** progression.

L3 ANSWER 28 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:107896 BIOSIS

DN PREV199800107896
TI Inhibition of apoptosis with Bcl-2 or BAG-1 promotes peritoneal dissemination of human gastric cancer cells.
AU Yawata, A.; Adachi, M.; Okuda, H.; Itoh, F.; Kato, Y.; Hinoda, Y.; Yachi, A.; Imai, K.
CS First Dep. Internal Med., Sapporo Med. Univ. Sch. Med., Sapporo 060 Japan
SO Tumor Biology, (Sept., 1997) Vol. 18, No. SUPPL. 2, pp. 124.
Meeting Info.: Meeting on From Basic Cancer Research to Clinical Application held at the XXVth Anniversary Meeting of the International Society for Oncodevelopmental Biology and Medicine Montreux, Switzerland September 19-24, 1997 International Society for Oncodevelopmental Biology and Medicine
. ISSN: 1010-4283.
DT Conference
LA English
IT . . .
and Molecular Biophysics); Tumor Biology
IT Chemicals & Biochemicals
Bcl-2 protein gene: apoptosis inhibitor, tumor cell expression, peritoneal dissemination promoter; **BAG**-1 **protein gene**: apoptosis inhibitor, **tumor** cell expression, peritoneal dissemination promoter

L3 ANSWER 29 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:69792 BIOSIS
DN PREV199800069792
TI Characterization of the subcellular location of **BAG**-1 **protein** in human breast **cancer**.
AU Turner, B. C. (1); Krajewska, M.; Krajewski, S.; Wang, L. (1); Carter, D.;
Takayama, S.; Kochel, K.; Glazer, P. M.; Haffty, B. G. (1); Reed, J. R.
CS (1) Dep. Therapeutic Radiol., Yale Univ. Sch. Med., New Haven, CT USA
SO Breast Cancer Research and Treatment, (Oct., 1997) Vol. 46, No. 1, pp. 69.
Meeting Info.: 20th Annual San Antonio Breast Cancer Symposium San Antonio, Texas, USA December 3-6, 1997
ISSN: 0167-6806.
DT Conference
LA English
TI Characterization of the subcellular location of **BAG**-1 **protein** in human breast **cancer**.

L3 ANSWER 30 OF 32 CAPLUS COPYRIGHT 1999 ACS
AN 1997:124475 CAPLUS
DN 126:126901
TI Apoptin in induction of p53-independent apoptosis in transformed cells, use in tumor therapy, apoptin localization, and diagnostic test for cell-transforming activity
IN Noteborn, Matheus Hubertus Mari
PA Aesculaap B.V., Neth.
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9641191	A1	19961219	WO 1996-NL229	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2221495	AA	19961219	CA 1996-2221495	19960607
AU 9659136	A1	19961230	AU 1996-59136	19960607

EP 830604 [redacted] 19980325 EP 1996-916[redacted] 19960607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 11506340 T2 19990608 JP 1996-500327 19960607
US 5958424 A 19990928 US 1997-910618 19970813
PRAI US 1995-484939 19950607
NL 1990-2008 19900912
WO 1996-N
L229 19960607

AB The invention describes that apoptin fails to induce apoptosis in human normal cells, and that when normal cells are transformed, they become susceptible to the apoptin-induced apoptosis. Apoptin induces in various human tumor cells a p53-distinct type of apoptosis, and cannot be blocked by a variety of apoptosis-inhibiting agents. The invention comprises an anti-tumor agent which specifically kills tumor cells and not normal cells. It further provides the induction of cell death by means of gene therapy. Apoptin can induce apoptosis in non-human animal tumor cells. In normal cells apoptin was found predominantly in the cytoplasm, while in tumor cells it was located in the nucleus. The invention further comprises a diagnostic test for the detn. of cell-transforming activity.

IT Proteins (specific **proteins** and subclasses)
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**Bag**-1; apoptin in induction of p53-independent apoptosis in transformed cells, use in **tumor** therapy, apoptin localization, and diagnostic test for cell-transforming activity)

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	31	BAG near3 protein	USPAT	1999/12/21 16:11			0
2	BRS	L2	0	1 near30 (cancer or carcinoma or malignan$4 or tumor or tumour or metastis$4)	USPAT	1999/12/21 16:12			0
3	BRS	L3	12	1 and (cancer or carcinoma or malignan$4 or tumor or tumour or metastis$4)	USPAT	1999/12/21 16:13			0
4	BRS	L4	38	(bag near3 gene) or(bag-1n or bag-1m or bag-1l or bag-2 or bag-3 or bag-4 or bag-5)	USPAT	1999/12/21 16:14			0
5	BRS	L5	10	4 and (cancer or carcinoma or tumour or tumor or carcinoma or malignan$4 or metastasis$3)	USPAT	1999/12/21 16:15			0